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Hepatitis C Virus in Non-Hodgkin's Lymphoma. A Reappraisal After a Prospective Case-Control Study of 300 Patients

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It is widely thought, but not yet explained, that there might be a pathogenetic link between the infection of hepatitis C virus (HCV) and the onset of B non-Hodgkin's lymphoma (NHL). We studied the prevalence of serum anti-HCV antibodies among 300 NHL comparing it with the prevalence among 600 age- and sex-matched non-neoplastic subjects as controls, 247 patients with non-lymphomatous neoplasm, and 122 patients treated with immunosuppressive agents. We found a prevalence of 0.16 among NHL and 0.085 among controls and non-lymphomatous patients. Although the difference was statistically significant ($P < 0.001$), the odds ratio was 2.049 and its confidence intervals included the equality. The HCV prevalence was independent of NHL subset, and the genotypes distribution was the same among NHL and controls. We disclosed a HBsAg prevalence of 0.077 in NHL versus 0.008 in controls ($P < 0.001$) with an odds ratio of 9.9. We do not believe that these findings support the hypothesis of an HCV pathogenetic role in lymphomagenesis because (i) the risk of previous infection is marginally higher in NHL than in controls, (ii) a typical genotype distribution is lacking, as is a NHL clinico-histological feature associated with HCV, and (iii) the higher prevalence of viral infection is not specific as witnessed by the high HBsAg prevalence. Am. J. Hematol. 64:95–100, 2000.

Key words: hepatitis C virus; hepatitis B virus; non-Hodgkin's B cell lymphoma; lymphomagenesis

INTRODUCTION

Both the evidence of a strict association between hepatitis C virus (HCV) and mixed cryoglobulinemia (MC) [1,2], and the observation that sometimes MC can evolve to low-grade lymphoma [3] suggest a possible role of HCV in the pathogenesis of B-cell non-Hodgkin's lymphomas (B-NHL) [4]. This hypothesis is supported by evidence of HCV lymphotropism [5,6] as well as by the demonstration of HCV-specific genomic sequences in pathologic lymph node tissue [7]. At present, however, a possible pathogenetic role of HCV in human lymphomas is based on epidemiological data only [8].

A high frequency of HCV infection among B-NHL patients (excluding chronic lymphocytic leukemia, hairy cell leukemia, Waldenström's macroglobulinemia and

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multiple myeloma) has been reported in Italy (451 HCV-positive among 1715 B-NHL) [3,4,7–16], Japan (6 of 65 patients) [17], USA (32 of 130 patients) [18], and Venezuela (7 of 94 patients) [19], while the frequency of HCV infection is quite insignificant in the United Kingdom (1 of 268 patients) [20–22].

To date, few studies have assessed the frequency of anti-HCV antibodies in a large series of B-NHL. These studies, however, lack a cohort of healthy subjects matched for sex and age as controls, essential to determine the frequency of anti-HCV antibodies in a healthy comparable population.

The aim of this study is to evaluate the frequency of serum anti-HCV antibodies positivity in a large series of B-NHL and to compare it with those observed in a group of healthy subjects, in a group of patients with non-lymphoid malignancies and in a group of immunosuppressed patients.

PATIENTS AND CONTROLS

Study Population

From 01/01/96 to 30/06/97, 300 consecutive patients with diagnosis of B-cell NHL (145 men, 155 women; median age 63 years, range 17–92) were included in the study regardless of their performance status, stage, and grade of disease.

They were Italian-born, human immunodeficiency virus negative, heterosexuals, with no history of intravenous drugs or alcohol abuse. None of them had received interferon treatment. All were newly diagnosed patients, observed at eleven institutions in Lombardy (Northern Italy). Other B-cell neoplasms (B-cell chronic lymphocytic leukemia, acute leukemia, multiple myeloma, Waldenström's macroglobulinemia), T-cell and putative natural-killer-cell neoplasms, and Hodgkin's disease were not included. The study population excluded patients with previous or concomitant solid neoplasm, other hematological malignancies, or autoimmune disorders. According to the REAL classification there were 8/300 (2.6%) with lymphoplasmacytoid lymphoma/immunocytoma and 16/300 (5.2%) with MALT lymphoma.

Control Groups

(1) Internal and surgical diseases. This group included 600 unselected patients age- and sex-matched with the study population: 290 men and 310 women; median age 64 years (18 to 92). The cases were consecutively recruited during their routine visits at medicine, surgery, or traumatology departments during the recruitment period of the study population. They were Italian-born, human immunodeficiency virus negative, heterosexuals, with no history of intravenous drugs or alcohol abuse. None of them had received interferon treatment. This group did not include any patient with hematological malignancies, overt liver diseases (cirrhosis or ascites), solid neoplasms, autoimmune diseases, or any patient who had been treated with corticosteroid or immunosuppressive agents.

(2) Neoplastic pathologies. This group included 247 consecutive patients: 122 men, 125 women, median age 62 years (27 to 89), with solid neoplasm (93/247 colon carcinoma, 85/247 breast cancer, and 69/247 lung cancer). They had recently undergone to surgical treatment. The criteria for inclusion were the same as in group 1.

(3) Autoimmune disorders. We consecutively recruited 122 unselected patients (14 men, 108 women, median age 59.5 years, range 18–92), with systemic lupus erythematosus and rheumatoid arthritis, treated with immunosuppressive drugs or corticosteroid for at least one year. The criteria for inclusion were the same as in groups 1 and 2.

MATERIALS AND METHODS

NHL Diagnosis

NHL was diagnosed by pathological biopsy, according to the Working Formulation (WF) for NHL and the Revised European American Classification of Lymphoid neoplasm (REAL), and by the immunophenotypic analysis of surface T and B lymphocyte markers.

Viral Assays

We used ELISA (Ortho HCV 3.0) and RIBA (Chiron RIBA HCV 3.0) tests for the detection of antibodies to hepatitis C virus, RT-"nested" PCR (sensitivity 200 copies/mL) for HCV-RNA and INNO-LiPA HCV II line probe assay for the genotyping of HCV.

For the detection of HBV surface antigen we used the ELISA, Organon-Technica test.

Statistical Evaluation

The study was planned as observational, multicenter, and prospective, according to the case-control model, with case/control ratio of 1/2 and matching for sex and age. We evaluated the differences of sex and age distribution among the patients with non-Hodgkin's lymphoma (NHL), non-lymphoid malignancies (NLM), or autoimmune disorders (AD), and the differences of frequencies of anti-HCV antibodies and HBV surface antigen (HBsAg) between sexes, among groups of cases (NHL, matched controls, NLM, AD), WF categories of NHL and four age classes: younger than 21, from 21 to 40, from 41 to 60, and older than 60.

Among the NHL patients bearing anti-HCV antibodies we studied the distribution of WF categories and the presence of extranodal lymphoma or involvement of stomach, liver, or bone marrow comparing these frequen-

cies with those of the same features in the whole NHL group and in the non-HCV subset.

We estimated the differences of age distribution among groups and between sexes with one-way ANOVA and performed the remaining evaluations by contingency tables and Pearson's χ^2 using Cochran's method to test the linear trend for the proportions.

We applied the odds ratio method to estimate the relative risk of HCV infection or HBsAg presence between NHL patients and controls.

We obtained two-sided 95% confidence intervals estimates for the proportions from *z* values and two-sided 95% confidence intervals estimates for odds ratios from the natural log of their standard error.

We used BMDP Statistical Software package release 7 for statistical evaluations and nQuery package release 2 (Statistical Solution Ltd) for confidence interval assessment and power study.

RESULTS

The power of our study ranks 0.88 for anti-HCV evaluation and 0.99 for HBsAg evaluation under an α error equal to 0.05.

The distribution between sexes is the same among NHL (M/F = 1/1.07) and NLM (M/F = 1/1.02), but females occur more frequently among AD (M/F = 1/7.71) with a significant ($P < 0.001$) difference.

The difference in age distribution varies significantly ($P < 0.012$) among groups, the younger classes being more frequent in AD (median age = 59.5; C.I. 18–82) and the older in NLM (median age = 62.5; C.I. 27–89).

We found anti-HCV antibodies in the sera of 48 NHL, 51 controls, 15 NLM, and 6 AD. Among these anti-HCV bearing persons, 7 NHL, 4 controls, and 3 NLM reported previous transfusions, with a prevalence of 0.12 (C.I. 0.06–0.18) in the overall series of anti-HCV-positive subjects.

Anti-HCV is more frequent in NHL (0.16; C.I. 0.119–0.201) than in controls (0.085; C.I. 0.063–0.107), NLM (0.085; C.I. 0.031–0.091), and AD (0.049; C.I. 0.011–0.087) ($P < 0.001$), and the confidence interval in NHL is clearly separate from other groups' intervals which overlap.

A NHL patient shows a risk of bearing anti-HCV antibodies 2.049 times higher (C.I. 0.701–27.027) than a matched control.

We found HBsAg in the sera of 23 NHL, 5 controls, 9 NLM, and 2 AD, none of them had history of transfusion.

The HBsAg is significantly more frequent in NHL (0.077; C.I. 0.047–0.107) and NLM (0.036; C.I. 0.013–0.059) than in controls (0.008; C.I. 0.001–0.015) and AD (0.016; C.I. limit below 0) ($P < 0.001$), and the risk of bearing this antigen is 9.9 times higher in NHL than in matched controls (C.I. 3.7–26.2).

In NLM the lower confidence limit for the risk of HBsAg presence overlaps with the upper limit of controls, and the upper limit of NLM overlaps with the lower limit of NHL; the AD series is too small for a sound evaluation of confidence interval for this feature.In the series as a whole the anti-HCV frequency is similar between the sexes ($P < 0.34$) and it is significantly higher among the older subjects ($P < 0.001$).

Among NHL patients, sex ($P < 0.9$), age classes ($P < 0.24$), anti-HCV ($P < 0.1$), and HBsAg ($P < 0.63$) frequencies are uniformly distributed among WF categories, as shown in Table I.

Differently from the whole series, the anti-HCV distribution does not differ among age classes ($P < 0.33$) but a linear trend between frequency and age classes shows a weak significance ($P < 0.06$).

No link is found between HCV and the extra-nodal lymphoma ($P < 0.62$) or the involvement of marrow ($P < 0.4$) or stomach ($P < 0.71$) but the liver involvement is more frequent in the HCV group ($P < 0.02$), as reported in Table II.

The distribution of WF categories does not differ between HCV-positive and -negative NHL patients ($P < 0.86$) nor does the frequency of MALT lymphoma ($P < 0.76$).

HCV-RNA has been detected, allowing genotype identification, in the serum of 86% of HCV-positive NHL patients and in the one of 79% of HCV-positive controls. The HCV genotypes are uniformly distributed between NHL patients and controls ($P < 0.51$): the 2a2c genotype is found more frequently both in NHL (0.55) and controls (0.46), genotype 1b shows a frequency of 0.325 among NHL and 0.462 among controls, and other genotypes (1a, 2, 3a, 4) are 0.125 in frequency in NHL and 0.077 in controls.

DISCUSSION

Our results confirm the association already reported between NHL and HCV and are in accordance with the latest and larger series which state that the anti-HCV antibodies frequency among NHL ranges from 0.1 to 0.2 [12,23].

The presence of cryoglobulins is rarer in our series than in the others, possibly for lack of patients with previous cryoglobulinemic syndrome, this finding being contemporary or closely connected with the NHL diagnosis.

We could not find a specific behavior of anti-HCV-positive NHL for WF categories or for organ involvement and the frequency of liver involvement has a weak significance, being very rare (Table II).

The genotype distribution pattern we have observed in NHL differs from that reported in hepatitis patients [24], but it mirrors what we found in the control group.

TABLE I. NHL Features

WF[a] categories	No.	M/F	Age median (min–max)	HCV Freq. (conf. int. 95%)	HBsAg Freq. (conf. int. 95%)
A, B, C	84	1/1.1	63 (29–89)	0.167 (0.087–0.247)	0.060 (0.009–0.101)
D, E, F	73	1/1.36	64 (17–92)	0.137 (0.058–0.216)	0.055 (0.003–0.107)
G, H, I, J	136	1/1.03	63.5 (19–92)	0.612 (0.100–0.224)	0.103 (0.052–0.154)
MALT	16	1/1.8	61.5 (50–75)	0.188[b]	0

[a]WF classification is available for 293 patients.
[b]Lower confidence limit below 0.

TABLE II. NHL Features Among HCV-Positive and HCV-Negative Patients

	HCV-positive NHL (48)		HCV-negative NHL (252)	
Feature (overall freq.)	Bearing feature	Freq. (conf. int. 95%)	Bearing feature	Freq. (conf. int. 95%)
Extranodal inv. (0.593)	30	0.625 (0.488–0.762)	148	0.587 (0.526–0.648)
Marrow inv. (0.283)	16	0.333 (0.200–0.466)	69	0.274 (0.219–0.329)
Stomach inv. (0.067)	2	0.042[a]	18	0.071 (0.039–0.103)
Liver inv. (0.030)	4	0.083 (0.005–0.161)	5	0.020 (0.003–0.037)
Cryoglobulins (0.033)	3	0.063[a]	7	0.028 (0.026–0.030)
Age to 20 (0.007)	0	0	2	0.008[a]
Age 21–40 (0.090)	2	0.042[a]	25	0.099 (0.062–0.136)
Age 41–60 (0.300)	12	0.250 (0.128–0.372)	78	0.310 (0.253–0.367)
Age >60 (0.603)	34	0.708 (0.579–0.837)	147	0.583 (0.522–0.643)
WF A, B, C[b] (0.286)	14	0.304 (0.071–0.437)	70	0.283 (0.227–0.339)
WF D, E, F[b] (0.248)	10	0.217 (0.098–0.336)	63	0.255 (0.201–0.309)
WF G, H, I, J[b] (0.464)	22	0.478 (0.334–0.622)	114	0.462 (0.400–0.524)
MALT (0.053)	3	0.062[a]	13	0.052 (0.022–0.082)

[a]Lower confidence limit below 0.
[b]WF classification is available for 293 patients.

We found a prevalence of HBsAg significantly greater in the NHL group than in nonmalignant controls, although this difference is smaller if compared with the NLM group. These findings are quite different from those currently reported, but the published papers frequently refer to ill-chosen controls such as groups different in size from the NHL group, or drawn from the general population or from blood donors [12,25], without correction for the nonrandom differences existing among these populations and NHL patients. The studies rarely report the power of the analyses, therefore an evaluation of their conclusions could be defective.

The link between the contact with HCV and some histological subsets or with more aggressive behavior of the lymphoma is irregularly found [10,12,15,16,23,25–29] probably because of the unreliable size of the series.

On the other hand, the reported differences in the genotypes distribution pattern between NHL and patients with chronic liver disease are useless to define their pathogenetic role because these patients had active hepatitis and were selected for Interferon treatment after hepatic biopsy: those with silent HCV infections or hepatic cirrhosis, and those over a certain age were excluded from this assessment. Our findings show that the genotype pattern of NHL patients is the same as the one in non-neoplastic controls and suggest that, from this point of view, chronic hepatitis patients are those who differ from the normal population [24].

The lack of references to HBsAg indicates that the published series are too small to allow judgment of a possibly rare but significant finding.

The differences among anti-HCV frequency in NHL, in NLM and in the group of patients treated with immunosuppressive therapy are too small to prove the hypothesis of a pathogenetic role of the virus for NHL. Many authors mention the possibility that HCV can induce NHL, but to date no study has demonstrated this [4,11,12,16,23]. The lymphotropic behavior of this virus and its ability to induce a activation of the immune system [30,31] make a lymphoma-inducing capacity likely but not proven. The finding of viral RNA in lymphomatous material [7] is not enough to demonstrate this, because its lymphotropism makes the HCV presence foreseeable in organs with high lymphocyte traffic, and in situ hybridization hardly ever has shown the virus genomic material inside the neighboring epithelial or lymphoid cells [7,32] and very rarely inside the lymphoma cells [28].

The epidemiological arguments advanced to support the lymphomagenic activity are weakened by the high

variability of study populations. Being the virus endemic in some areas and sporadic in others, the local virus prevalence closely parallels the prevalence of the cryoglobulinemic syndrome, in which the viral RNA is hardly ever present, but follows neither NHL prevalence nor the prevalence of the low-grade categories within lymphomas. This finding is in accordance with a model assuming the HCV as inducer of cryoprecipitation, not as lymphomagenesis agent. On the contrary, the frequency of anti-HCV antibodies among NHL mirrors the local prevalence in the general population [17,21,33,34], as if the lymphoma patients may act as a reservoir for a virus, common and easily growing in the lymphoid tissue independently of its oncogenic power. This hypothesis is supported by the prevalence of infection from HBV, higher than in the control group and possibly more than HCV prevalence itself, and by the observation that also the HBV has a tropism to mononuclear blood cells [35–39].

Occasional patients suffering from chronic hepatitis have been reported to develop NHL with exclusive liver involvement [19,40,41] and some series of patients with HCV-related liver disease have been reported to have a greater risk of developing NHL [42]. Liver involvement, however, is not rare and the regular echographic monitoring in hepatopathic patients facilitates its early diagnosis and acts as a confounder if the unmonitored general population is assumed as control. A confounder may arise also in the evaluation of lymphoma prevalence among patients with chronic liver disease, when the general population is assumed as control. The age-range in liver patients and the one observed in lymphoma patients largely overlaps, but the former is different from that observed in the community. We found a significant relation between HCV infection and the middle and old ages, the age groups with the highest lymphoma prevalence. Nevertheless this parallelism does not reveal a causal link: even if the statistical significance is lost, the same trend is present in the NHL group, meaning that the linkage between HCV infection and age group could be stronger than the linkage between HCV infection and lymphoma.

The studies assuming control groups other than the general population can not confirm the finding of a relation between HCV infection and NHL; a retrospective study revealed an increase of NHL in a group of patients with liver cirrhosis, but none of these had HCV-related liver disease [43]. Furthermore, in a large series of HCV-related chronic hepatitis the ratio of frequencies of NHL and Hodgkin's disease were similar to those found in the community [44].

We conclude that among NHL the prevalence of HCV infection is higher than in non-neoplastic people and in patients with non-lymphoproliferative malignancies or receiving immunosuppressive treatment. This difference cannot be attributed to a generic malignancy or to a depressed immune competence. The small difference among these groups, the identical genotype pattern between NHL and controls and the contemporary finding of a similar increase in the HBV virus do not support the hypothesis that HCV plays a role in lymphomagenesis.

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